REMARKS

Reconsideration of this application is respectfully requested. Claims 1-3 have been canceled without prejudice or disclaimer. Claims 4, 5, 8, and 11 have been amended to improve clarity and correct dependency, as detailed below. No new matter has been added by way of these amendments. Claims 4-11 are pending and at issue.

Priority

Submitted herewith is a certified English translation of the priority document, i.e., Japanese Patent Application No. 2002-198941, which was filed on July 8, 2002 (**Attachment A**). Applicants respectfully request that the certified translation be considered by the Examiner, and that the priority document be made of record in this application. Upon entry of the priority document, the effective filing date for the present claims will be July 8, 2002.

Rejections under 35 U.S.C § 112, second paragraph

Claims 1-11 have been rejected under 35 U.S.C § 112, second paragraph, as indefinite. According to the Examiner, it is unclear what the phrase "a promoter from human telomerase" encompasses because human telomerase is a *polypeptide*, and a promoter is a *polynucleotide* (*see* Office Action, page 3).

Claims 1-3 have been canceled, thereby rendering the rejection moot as to these claims.

Without conceding the accuracy of the rejection, claim 4 has been amended to recite "*A polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order.*" Support for this amendment is found in original claims 1-3 and throughout the specification, for example, in Figure 1. In view of the cancellation of claims 1-3 and the amendment of claim 4, the allegedly indefinite phrase has been removed, and the rejection is moot. Applicants therefore respectfully request that this rejection be withdrawn, accordingly.

Rejections under 35 U.S.C § 112, first paragraph

Claims 1-11 have been rejected under 35 U.S.C § 112, first paragraph, as lacking enablement. According to the Examiner, the specification does not reasonably provide enablement for: 1) a method of treating cancer *in vivo*; 2) a polynucleotide comprising a promoter from any human telomerase gene; or 3) the use of the claimed nucleic acid wherein the E1 gene is not operably linked to a promoter to cause expression (*see* Office Action, page 4). The Examiner further contends that original claims 8-11 lack enablement because no step is recited in the claims (*see* Office Action, page 5).

Claims 1-3 have been canceled, thereby rendering the rejection moot as to these claims.

Without conceding the accuracy of the rejection, claim 4 has been amended to recite "A polynucleotide comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order." Support for this amendment is found throughout the specification. For example, such a polynucleotide and its manufacture are disclosed in Example 1 and Figure 1 of the specification. In view of the guidance provided by the specification, a person of ordinary skill in the art would not require undue experimentation to manufacture the polynucleotide of claim 4.

Additionally, claims 8 and 11 have been amended to recite a method comprising a distinct step (i.e., step (a)). Support for these amendments is found throughout the specification, for example, in the published application (U.S. Patent Publ. No. 2006/0239967) at paragraphs 0017, 0041, 0039-0049, and in Example 6. In view of the claim amendments, and further in view of the cited disclosure, a person of ordinary skill in the art would be able to carry out the claimed method without undue experimentation because adequate guidance is provided both in the description and by way of working examples.

The Examiner states that the claimed method further lacks enablement because the use of viral polynucleotides in gene therapy has continued to be unpredictable and inefficient for the last decade (*see* Office Action, page 5, wherein the Examiner cites: **Pouton**, et al., *Adv. Drug*

Deliv. Rev., 46(1-3)187-203 (2001); **Johnson-Saliba**, et al., *Curr. Drug Targets*, 2(4):371-399 (2001); **Read** et al., *Adv. Genet.*, 53:19-46 (2005); and **Dobson**, *Gene Ther.*, 13(4)283-287 (2006)). Applicants submit, however, that the methods recited in claims 8-11 are not directed to gene therapy, as alleged by the Examiner, which is the focus of the cited references.

Pouton, Johnson-Saliba, Read, and Dobson each disclose *in vivo* gene therapy methods that use non-viral vectors. The non-viral vectors induce tumor cell death by inducing the expression of another gene, i.e., a therapeutic gene. Importantly, such non-viral vectors are not necessarily capable of inducing tumor cell death by the mere presence of the vector *per se* within the tumor cell. Thus, *in vivo* gene therapy methods that rely upon the activation therapeutic genes by vector activation, such as those disclosed in the cited references, are illustrative of difficulties including vector targeting, efficiency of gene delivery, and other obstacles noted by the Examiner.

In contrast, the claimed oncolytic virus is capable of replicating selectively in tumor cells and inducing tumor cell death without requiring the further expression of a different therapeutic gene. In other words, the present invention kills tumor cells using an entirely different mechanism, i.e., the proliferation of the virus *per se* within a tumor cell resulting in tumor cell death. The claimed method does not require additional desired (therapeutic) genes to be expressed to induce cell death. For this reason, i.e., because the expression of the claimed virus within a tumor cell will kill the tumor cell without the need for the expression of a therapeutic gene, the claimed invention is not subject to the same difficulties as those disclosed in the cited references. Furthermore, because of these different mechanisms, the cited references are not applicable to the claimed method. The present claims are enabled based on the present disclosure which includes working examples (e.g., Example 6) and guidance on administration doses (*see* ¶ 0044). Undue experimentation would therefore not be required to carry out the claimed method which is distinct from the methods disclosed in the cited references.

Finally, the Examiner states that the specification fails to provide adequate disclosure regarding: (i) the genes that are to be expressed by the hTERT promoter; (ii) the routes of administration of the recited virus; (iii) the technical considerations required for initiation of the

expression of a given therapeutic gene of interest and sustenance of sufficient expression level for treating a given cancer of interest; and (iv) how the immune responses resulting from introduction of adenovirus are minimized in terms of what part of adenovirus genome of the recited adenovirus remains in addition to the recited E1 gene.

Applicants submit that with respect to (i), the gene (cassette) to be expressed by the hTERT promoter is an E1 gene having an E1A gene, IRES sequence, and an E1B gene in this order (*see* specification, ¶¶ 0023, 0027, and 0030). With respect to (ii), the routes of administration are disclosed in ¶ 0041 and Example 6. As to (iii), the claimed method does not require the expression of a therapeutic gene (as discussed *supra*). Finally, as to (iv), any known suitable immunosuppressant can be used (*see, e.g.,* ¶ 0045).

Applicants note that even "[A]n extended period of experimentation may not be undue if the skilled artisan is given *sufficient direction or guidance*" (*see In re Colianni*, 561 F.2d 220, 224, (CCPA 1977) (emphasis added). The test is not merely quantitative, since "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*see In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). In view of the supportive disclosure that provides ample guidance for making and using the claimed invention, a person of ordinary skill in the art would be able to arrive at the claimed invention without requiring undue experimentation. Applicants therefore respectfully request that the rejections be withdrawn.

Rejections under 35 U.S.C § 102(b)

Claims 1-3, 5-8, and 11 have been rejected as anticipated by Morin, et al. (WO 00/46355) ("Morin") for the reasons set forth on pages 9-10 of the present Office Action.

Claims 1-3 have been canceled thereby rendering the rejection of these claims moot.

Applicants submit that in order for a reference to anticipate the claims under § 102(b), the reference must disclose each and every limitation of the claimed invention, and must be an

embodiment of the claimed invention. *Dana Corp. v. Am. Axle & Mfg., Inc.*, 61 USPQ2d 1609 (Fed. Cir. 2002). The teaching must clearly disclose the invention with a certain degree of precision, without the need for picking and choosing components. *Ex parte Westphal*, 223 USPQ 630 (Bd. Pat. App. 1983).

Without conceding the accuracy of the Examiner's rejection, claim 4 has been amended to call for "A polynucleotide cassette comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order." Applicants submit that Morin fails to teach each limitation of amended claim 4, and thus, Morin does not anticipate the invention recited in claim 4 and dependent claims 5-11. Applicants therefore respectfully request that these rejections be withdrawn.

Rejections under 35 U.S.C § 102(a) and § 102(e)

Claims 1-3 and 5-11 have been rejected as anticipated by U.S. Pat. Publ. No. 2003/0104625 ("Cheng"). According to the Examiner, Applicants cannot rely on the Japanese priority application (i.e., Japanese Patent Application No. 2002-198941, filed July 8, 2002) because a translation thereof has not been made of record in accordance with 37 C.F.R. 1.55 (*see* Office Action, page 10).

A certified English translation of the priority document is submitted herewith (*see* **Attachment A**).

Cheng first published on June 5, 2003, almost one year after the July 8, 2002 filing date of Applicants' Japanese priority document. Thus, Cheng is not available as a prior art reference against the present application in view of Applicants' Japanese priority document.

Even assuming that Cheng is available as prior art under § 102, which Applicants do not concede, Cheng does not disclose "A polynucleotide comprising an hTERT promoter, an E1A gene, an IRES sequence, and an E1B gene in this order," or methods of using such a polynucleotide, as is presently claimed. Applicants therefore respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C § 103

Claims 1 and 4 have been rejected under 35 U.S.C § 103 as obvious over Morin in view of Li, et al., *Cancer Res.*, 61(17)6428-6436 (2001) ("Li"). According to the Examiner, it would have been obvious to a person of ordinary skill in the art to combine Morin, which discloses cell and tissue specificity of the hTERT promoter and its transcriptional regulation in an adenovirus, with Li, which discloses a bicistronic cassette in an adenovirus 5 vector (Ad5) that harbors an E1A gene, an IRES sequence, and an E1B arranged in E1A-IRES-E1B order (*see* Office Action, page 14). The Examiner contends that a skilled artisan would be motivated to make the combination because the hTERT promoter taught by Morin activates transcription specifically in tumor cells, and the IRES taught by Li in an Ad5 vector controls the expression of E1A and E1B at the translational level.

Claim 1 has been canceled rendering the rejection of this claim moot.

For a claim to be obvious under 35 U.S.C. § 103, three criteria must be satisfied: i) there must be some suggestion or motivation to combine or modify the cited references; ii) there must be a reasonable expectation of success of combining or modifying the cited references; and iii) the combined references must teach each and every limitation of the claimed invention. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). Applicants submit that in contrast to the Examiner's position, there would have been no motivation to alter the teachings of Morin and Li to arrive at the claimed invention.

Morin does not teach or suggest the claimed polynucleotide cassette with IRES inserted between E1A and E1B. Therefore, the skilled artisan would not have been motivated to insert IRES between E1A and E1b, as presently claimed.

Additionally, Li does not disclose or suggest using hTERT promoter such as described in Morin. Even if a skilled artisan reading Li decided to replace the AFP TRE with a different promoter, there would have been no reasonable expectation that specifically replacing

AFP TRE with hTERT would be successful, or any expectation that such a replacement would be advantageous, particularly in view of the large number of potential promoters that could be utilized in such a system. In other words, there is no particular teaching in Li that would have lead a skilled artisan to specifically replace the AFP TRE with the hTERT promoter disclosed in Morin; a skilled artisan would have had no motivation to make such a replacement based on these two references alone.

Finally, the claimed polynucleotide results in unexpected and advantageous effects that would not have been predicted by a person of ordinary skill in the art. Specifically, the HCC-specific oncolytic adenoviruses taught by Li replicate only in specific types of cancer cells. In contrast, the claimed virus can be successfully utilized in a variety of different cancer cell types, wherein cell death is induced. Thus, the claimed virus can be used in the treatment of several different cancer types. Such an advantage is not suggested by the cited references.

In view of the foregoing, Applicants respectfully submit that the claimed invention would not have been obvious in view of the cited references. Therefore, the rejection should be withdrawn, accordingly.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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ATTACHEMENT A